Clinical Trials Management: Best Operational Practices & Compliant IT Solutions

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Agenda

- A review of the commercial product development lifecycle & business functions
- Industry ‘best practices’ for clinical operations
  - The make-up for a compliant environment
    - People, process & technology
  - Take away for IT solution compliance
- Addendum

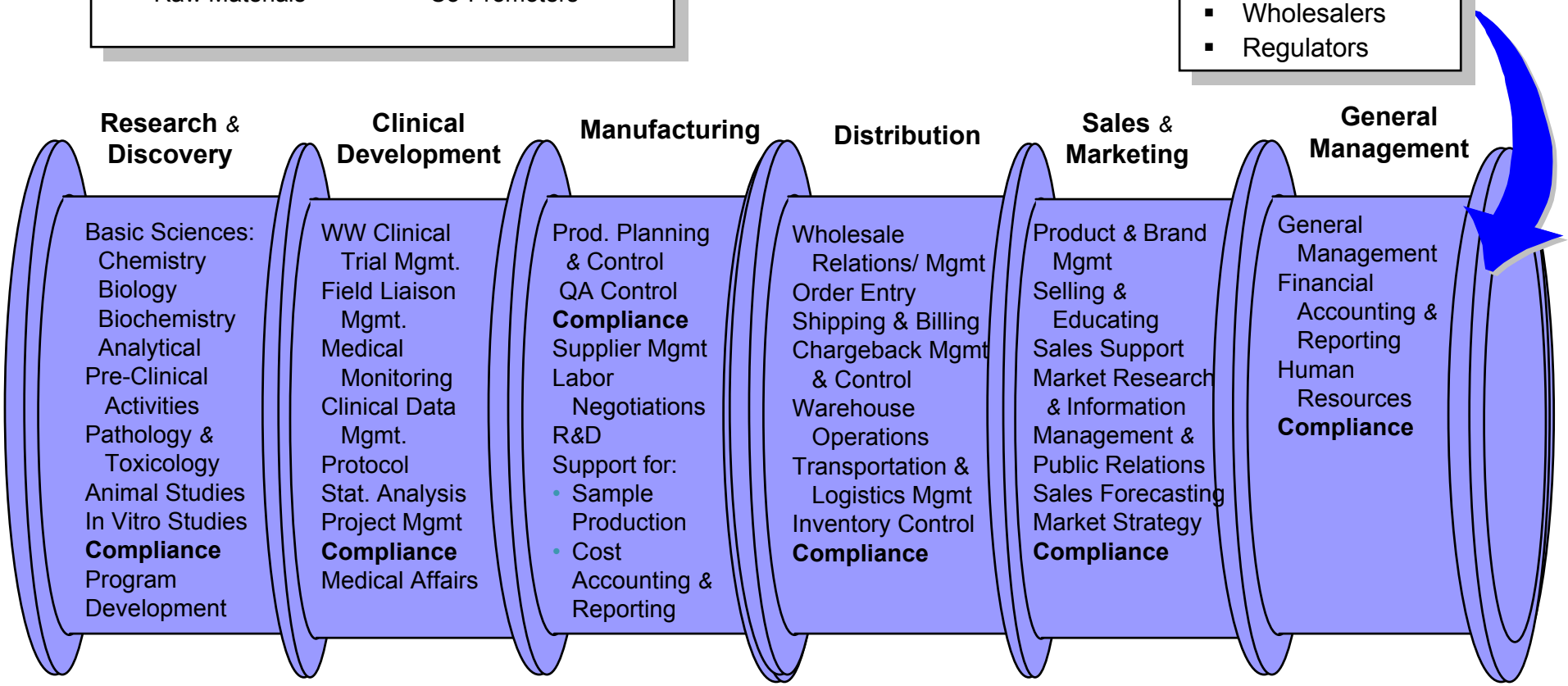
Commercial Product Development *Lifecycle*

INPUTS

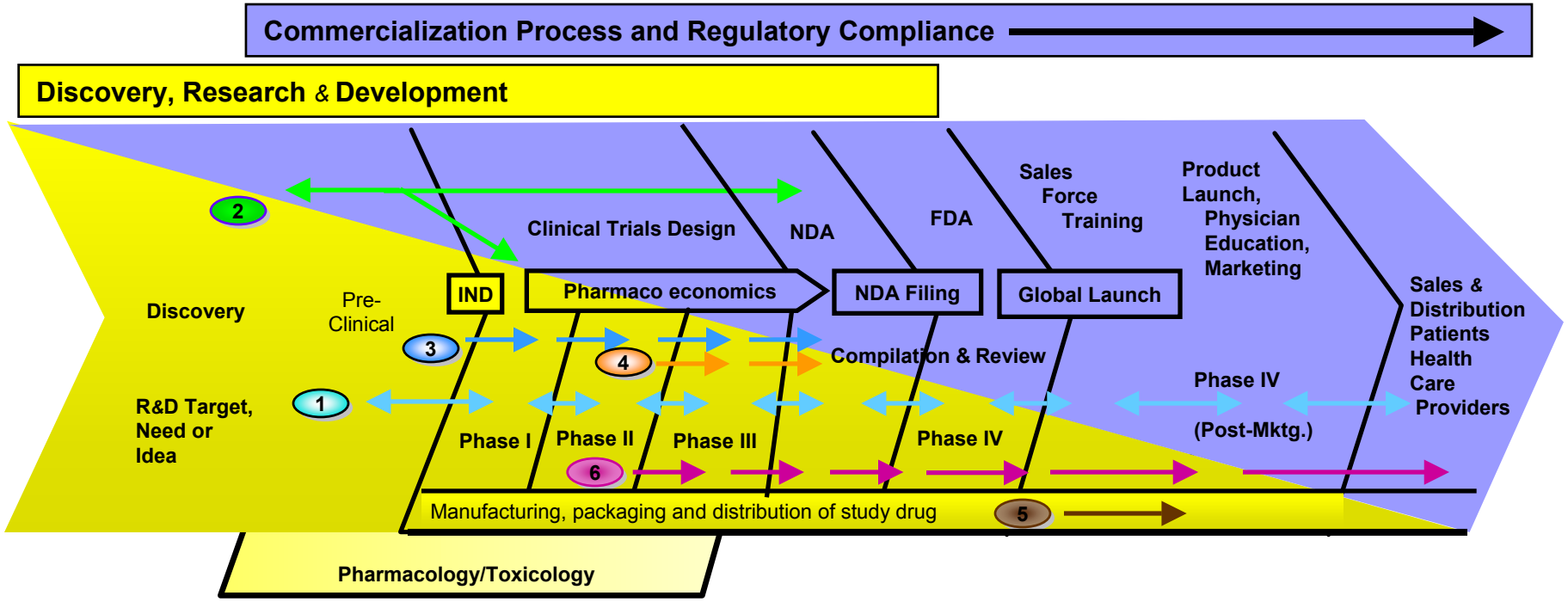
- External Information
- Human Resources
- Raw Materials
- Licensed Compounds
- Market Needs
- Co-Promoters

CUSTOMER INTERFACES

- Doctors
- Pharmacies
- Hospitals
- Managed Healthcare Organizations
- Wholesalers
- Regulators

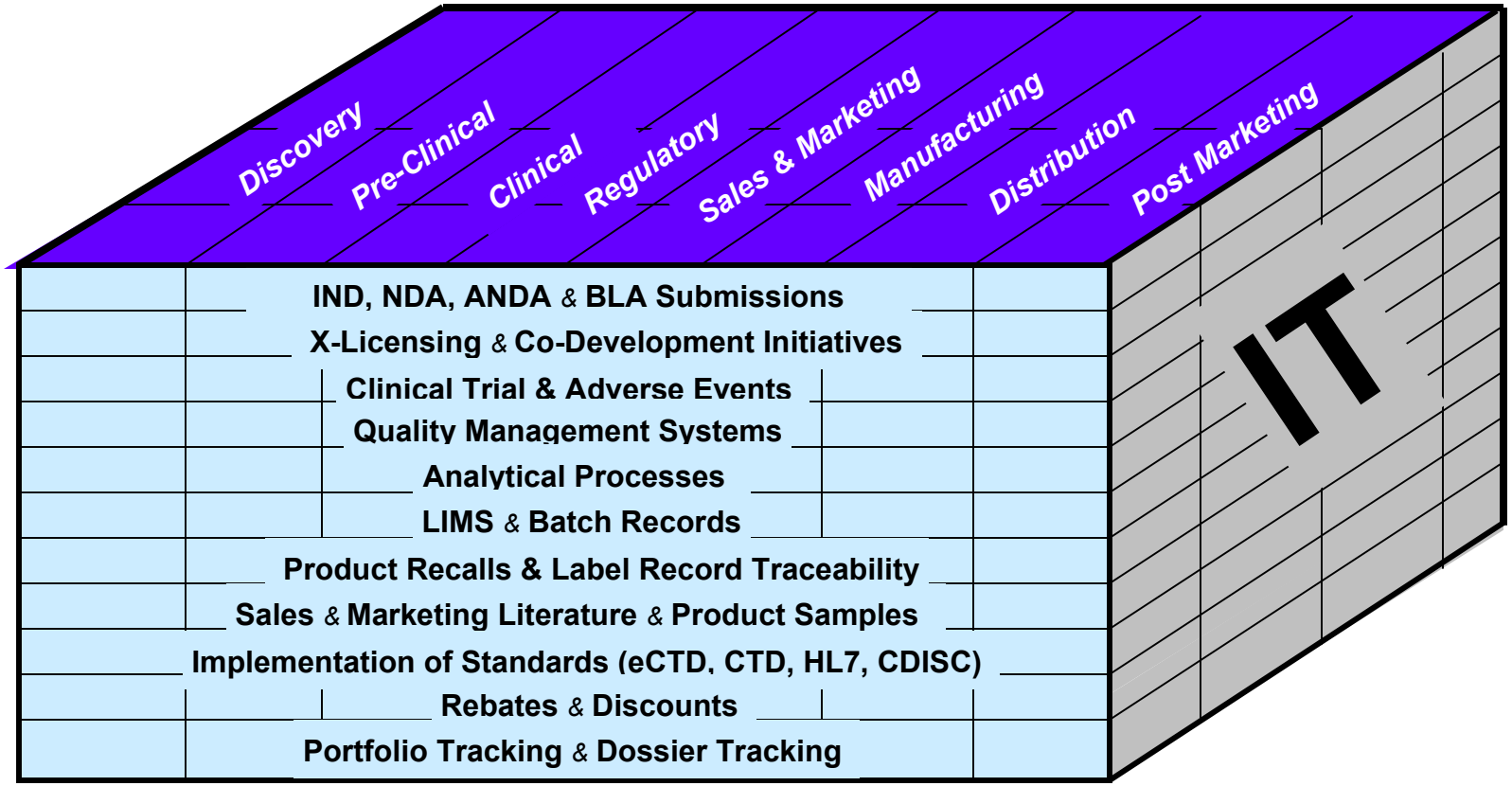


Regulatory compliance encompasses the entire product development lifecycle

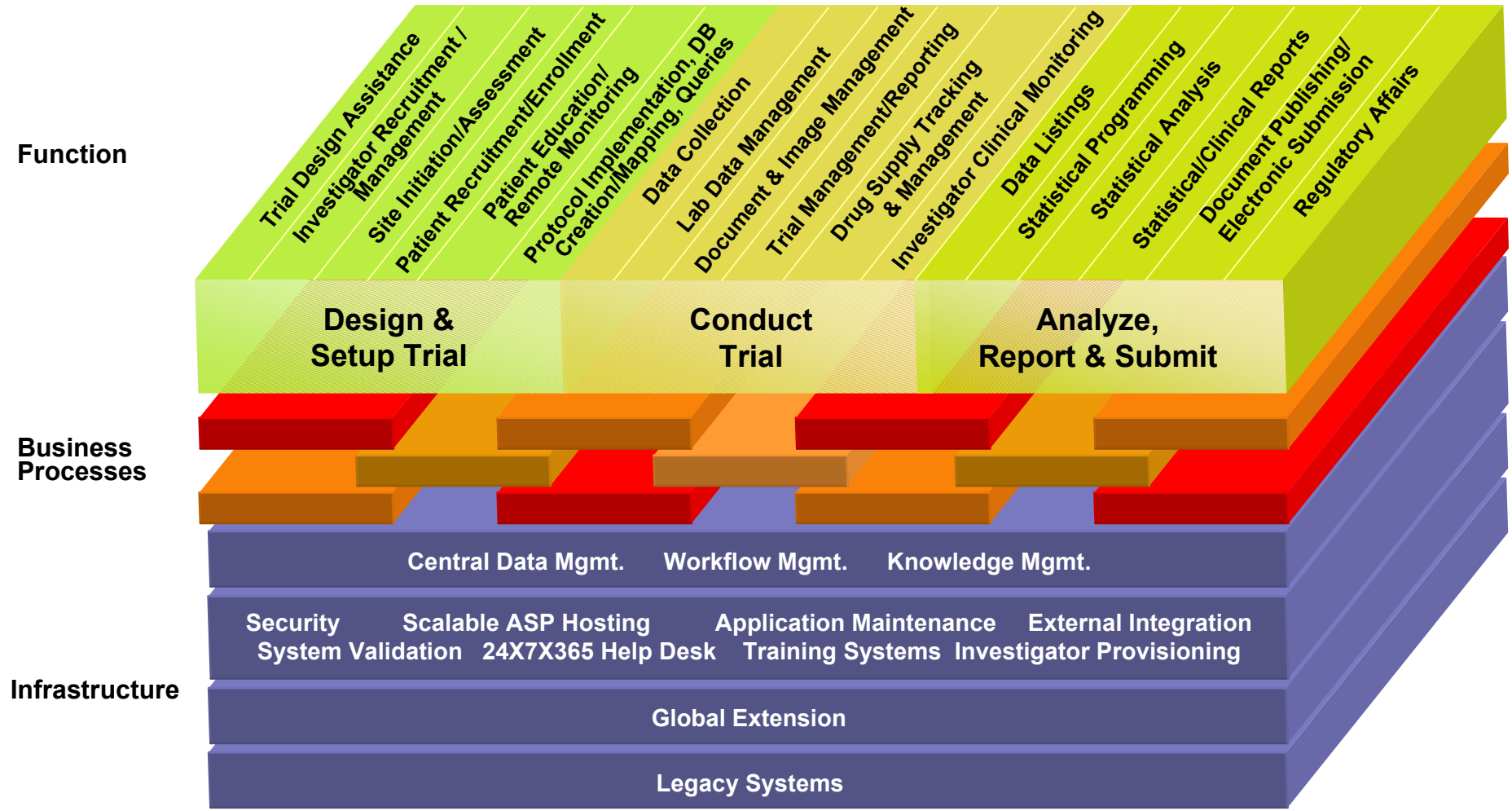


1. Basis of innovation
2. Commercializations (Alliances/Own)
3. Clinical Trail Decision-making/PharmacoVigilance
4. Submission intelligence (commercialization dependent)
5. Procurement intelligence
6. Channels Customization / Physician & Patient information

Compliance is a driver for IT activities across the entire value chain



An optimal, integrated model



Industry “Best Practices” for a Compliant Clinical Operations Environment

Clinical Trial Management

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•No formally recognized trial manager role •Projects differentiated only for line management responsibility	•Recognition of need for specific role of "trial manager" who is accountable for success	•Trial Manager role established •Consistent approach across projects with formal training in techniques	•Task estimates to complete are maintained and used to revise plan	•Dash-board gives daily updates on status of all trials •Projects tracking is used to prepare future plans
Outcome	•No formal "owner" of projects with ultimate accountability •Notion that compliance is only applicable to manufacturing systems	•Project management techniques used but inconsistent across projects •Some recognition compliance might be important to clinical IT systems	•PM software used •Staff reports status, time, expenditures, etc. manual •Compliance for IT systems raised to the Sr. Mgmt level	•Deviations from plan are identified in a timely manner •Runaway projects rare •IT systems compliance a std component of CT Mgmt.	•Runaway projects do not occur •Recognition all IT components of Clinical Trials are required to be compliant

Clinical Data Capture

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•*Ad hoc* encoding on a study by study basis	•Action plan to speed up data collection and data cleaning	•Recognition, continuous data collection & data cleaning is crucial to reduce data base close time	•Integration of other data collection tools (*e.g.* diary cards)	•Daily global data entry
Outcome	•Delayed file management •IT solutions not addressing Part 11 •No internal expertise for compliant clinical system development	•Try to find a new system of CDC •Continued disregard for Part 11 •Compliance still not considered a clinical issue	•Data management system in place with weekly or bi-weekly data Loads •Awareness Part 11 requirements, still unsure of appropriate approach	•Constant data cleaning and immediate feedback to investigators •Addressing Part 11 for all clinical systems is part of the CDM Plan	•Data available real time & usable •Database closed within 72 hours •All CDM systems are Part 11 compliant

Remote Data Entry

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•No experience with electronic data capture	•Need to increase data quality and speed of data collection recognized •Reviewed different vendor solutions	•Piloted remote data entry solution in one or more projects •Project by project data transfer to CDMS	•Defined strategy for using new technology (*e.g.* RDC integrated in IS environment, use of web based technology, *etc.*)	•Regular exchange of data and information among investigators, study monitors and project managers
Outcome	•Paper support •IT solutions not considered a solution	•No RDC studies started yet •Discussions begin re. IT solutions •Not fully aware of IT requirements of compliance	•Trials that benefit most from electronic data collection are identified •Search for IT solutions compliant with Part 11	•Established program to support RDC according to chosen strategy established •Recognize importance for compliant IT solutions	•Regular status reports automatically available •All RDE IT solutions are Part 11 compliant

Data and Coding Standards

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•*Ad hoc* encoding on a study by study basis •Decentralized and uncontrolled coding process	•Need for standardization recognized	•Standards team established •Project based code libraries defined for most standard questions	•Standard authorization & version control handled at the regional level •Centralized Encoding of con meds, Procedures & AEs	•Global authorization & version control for standard elements
Outcome	•No standards for data formats (*e.g.* date/time) across studies •Part 11 not recognized as important	•Codes for simples choices such as yes/no defined •Part 11 awareness begins	•Standards chosen •Date/time formats agreed across all countries •Intl. compliance awareness, unsure about IT systems	•Standards used for a complete drug program •Intl. compliance a built-in component for coding, especially for IT systems	•Global standards defined & improved continuously •IT solutions for coding requires Part 11 compliance

System and Data Migration

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•Too busy to review system performance and/or user requirements	•Need to replace existing system recognized	•New systems evaluated •New system possibly ordered	•Clear requirements •Acceptance testing •Solid roll-out planning •Resources available	•Participate in vendor/partner programs •Established assessment center for new technologies •Dedicated skills & resources
Outcome	•Delayed in data migration •Compliance not address •Part 11 considered only for manufacturing system	•Some requirements for new system Defined •Part 11 considered, still internal, dissenting opinions on applicability	•No migration strategy •No internal expertise on Part 11 •No understanding on where to begin	•Plan for data migration in pace •Part 11 a requirement in IT solution assessments	•Continuous •Improvement •All IT solutions are Part 11 compliant •IT solutions seamless & compliant with Part 11

Data Sharing

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•Most study data are archived only at the end of the trial	•Problems due to lack of data pooling or sharing in the past •Need data sharing capability	•New systems evaluated •New systems considered for implementation	•Data are prepared to support electronic submission •User needs defined	•Supports epidemiological research across countries •eCTD capability
Outcome	•No data pooling or sharing •Part 11 not considered applicable to clinical systems	•Some requirements for new system defined •Part 11 awareness occurs	•No migration strategy in place •Part 11 seen as the driver for migration – migrate to Part 11 compliant systems	•Project clinical trial data pooled; warehouse permits drill down & exploration •Part 11 initiatives commence	•Sharing trials data across therapeutic area •On-line data sharing as data are collected & cleaned •All IT systems compliant

Data Warehousing

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•Never heard of the concept of data mgmt •Data, metadata not defined and the meaning is ambiguous	•Is aware of problems related to data collection & management •Recognition of the need for a more structured approach to data pooling and exploration tools	•No structured inflow and store process has been set up •Understanding the benefits of a structured and well defined DW	•A managed DW has been built •Structured inflow and store processes set up and controlled •The relevance of metadata is understood	•DW service levels defined and frozen •Most analysis needs solved by the DW •Metadata is under custody & easily accessible by any user
Outcome	•Data has no single source of reference •No recognition of Part 11 applicability	•Data analysis is limited to internal data •Aware Part 11 maybe applicable	•The potential of advanced exploration (*e.g.* data mining) is recognized •Begin understanding for Part 11 systems requirements	•Several ways of data exploration are available & accepted by users •Recognition IT compliant solutions are a requirement	•Data mining exercises have proven their business value •DW architecture is integrated with group ware and intranet into KM environ. •Part 11 compliant

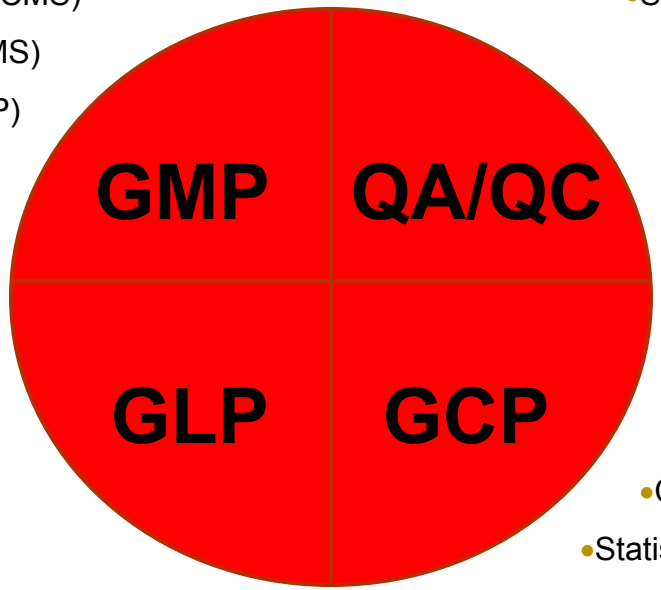
Take-away on compliance

- Compliance covers all business functions: The process, the people and IT solutions
- FDA considers compliance good business practices that provide them with the confidence that your company or research entity:
  - Understand your processes, your systems and your people
  - And that you are in control of all aspects of your business
- 75% of FDA citations (483's and Warning Letters) are issued for lack of appropriate procedures or failure to follow those procedures

Take away on 21 CFR Part 11 Compliance – Applicability!

- Manufacturing Execution Systems (MES)
- Maintenance Management Systems (MMS)
- Calibration Management Systems (CMS)
- Building Management Systems (BMS)
- Enterprise Resource Planning (ERP)
- Distributed Control Systems (DCS)
- SCADA Systems
- PLC Systems

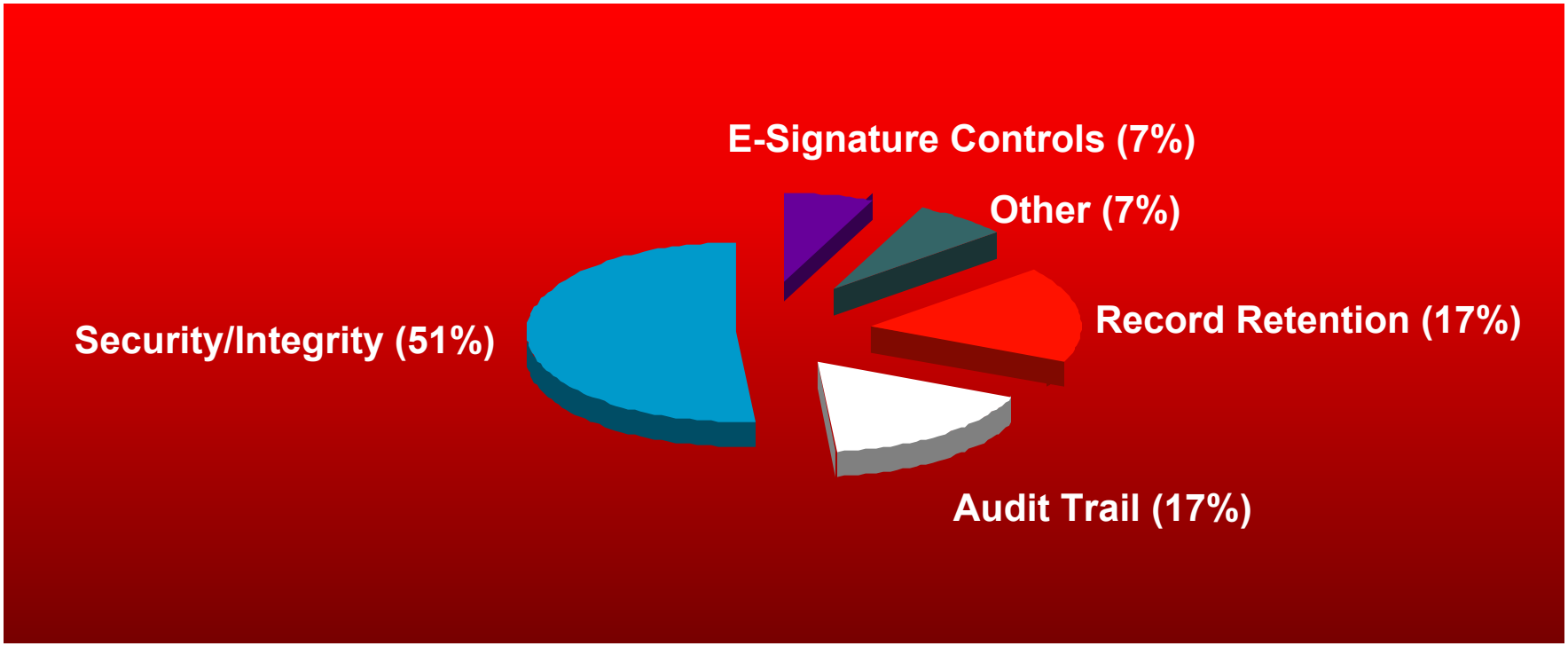
- Laboratory Information Management Systems (LIMS)
- Document Management Systems (DMS)
- Submissions Systems & Applications



- Stability Systems
- DM&PK Systems
- Toxicology Systems
- Laboratory Robotics Systems
- Environmental Monitoring Systems (EMS)
- Chromatography Data Acquisition Systems
- Laboratory Information Management Systems (LIMS)

- Case Report Form Systems
- Clinical Data Management Systems
- Statistical Analysis Software (*e.g.* SAS)
- Adverse Event Reporting Systems (AERS)
- Remote Data Entry/Remote Data Capture (RDE/RDC)
- Clinical Trial Management Systems (CTMS)
- Investigator Management Systems (IMS)
- Patient Registry (PR)

Take away on 21 CFR Part 11 Compliance – FDA Warning Letter & 483 breakdown



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Addendum

Business Vision & Compliance

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•Management does not have a clear, articulated and accepted vision for the future	•Vision exists within the minds of a limited set of senior people	•Need to establish a common vision	•Vision is formally presented and communicated •Vision includes compliance	•Vision is clearly articulated and has been committed to by the whole organization
Outcome	•There is no shared vision •No concept of the regulatory risk	•There are a number of different visions •Beginning awareness of the regulatory issues	•Creation of a vision team •Begin to address compliance - *ad hoc* basis only	•There are a number of versions of the one vision •Small pockets of non-compliance	•There is one, shared vision •Compliance becomes a part of the organizational culture

SOP Management

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•No quality systems in place •Poor understanding of GCP, EMEA/FDA guidelines	•Aware of relevant GCP requirements and regulations •Documentation exists but is out of date	•Recognition that employee commitment to GCP is impossible without people understanding "why"	•Quality systems are in place for each key area •Need to respect GCP is clearly and effectively communicated & linked to incentives	•Good interaction with regulatory authorities •Successful inspection with minor or no problems
Outcome	•No formal document management system (*e.g.* SOP's) •Compliance exposure is great	•Action plan to implement quality system •Compliance exposure remains significant	•Successful Inspections, minimal problems •Use of guidelines & Inspector Remarks to improve on compliance	•Successful inspections with limited Problems •Non compliance is minimal	•Quality systems in place and regularly Reviewed •Compliance risks remediated, continuous process improvement

Program Management

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•No formal PM process •Projects & initiatives but no structure or connection to or at the senior mgmt level	•Recognition , of need to set up a PM •Attempts to implement all "good ideas"	•Project initiated as separate events •Projects assessed individually on cost /benefit basis •Projects are discussed when issues need sr. mgmt input	•Concepts of program management exists •Major projects discussed at board-level meetings on a regular basis	•Individual projects are integrated w/i PM framework •Overall PM is regularly & frequently discussed at the board-level
Outcome	•Extreme lack of resource mgmt •"Seek & lynch" the guilty party •Compliance is not a critical component of project management	•Tug of war for resources to support important initiatives •Compliance is recognized as an issue but isolated recognition	•Sr. Mgmt. becomes involved •Compliance costs begin to be recognized •Compliance addressed at the project level only	•Formal structure emerges for PM •Compliance on work schedule & managed; compliance issues move up the ladder	•PM & Sr. Mgmt actively work to reduce compliance risks •Recognize compliance is important to a successful PM outcome

Drug Safety

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•AEs are •recorded in a multitude of databases, in several formats, across all countries •Reactive to regulatory obligations	•Pharmaco-vigilance seen as a cost	•Recognition that pharmaco-vigilance is more than regulatory compliance •Pharmaco-vigilance seen as a value add	•Managed centralized collection and evaluation process •Central or local reporting and response centers	•Ready for electronic reporting according to new EMEA and ICH guidelines
Outcome	•No audits •Regulatory risk of 'original record' and control over systems	•Audits generate lists of problems & opportunities •Organization begins to recognize risk	•Creation of an internal safety knowledge task force •Recognition safety issues lead to regulator intervention	•Safety knowledge maintained, built up •Safety recognized as just as important as product quality	•Pharmaco-vigilance part of proactive product life-cycle •Regulatory compliance is understood to be critical to pharmaco-vigilance

Document Management

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•No effective system in place	•File based systems •Multiple versions of documents generated (*e.g.* CRFs, SOPs)	•Archival system with version control in place	•Document management system incorporating necessary work flows established	•Knowledge about the documents permits easy retrieval & updating of relevant sections
Outcome	•Difficulty locating documents •Still paper based, no recognition of Part 11 requirements	•Documentation hard to find •Aware IT solution may be the answer •Still no awareness of Part 11 requirements	•Ability to treat the information (*e.g.* SOPs) •Part 11 awareness for IT solution	•Ability to pool one or more documents and to present one or more news documents •Part 11 accepted as a requirement for IT solutions	•Ready for electronic reporting according to new EMEA & ICH Guidelines •All IT solutions are Part 11 compliant

Data Cleaning

	Innocence	Awareness	Understanding	Competence	Excellence
Situation	•Data are cleaned many times •Checks are programmed after each study is ended •Paper cleaning process	•Cleaning operations are allocated to relevant persons •Poor investigators training	•Check libraries developed and used firm wide •Cleaning workflow optimized	•Quality is part of investigators evaluation and payment •Ongoing cleaning of data •Data checks integrated globally	•Last patient last visit and database locked in one day
Outcome	•Long time to solve queries •Poor data quality •Paper-based, no IT solutions considered	•Cleaning loops long but efficient •Awareness of Part 11, but not applicable to CDM systems	•Cleaning strategy defined •IT solutions considered, Part 11 considered	•Drastic reduction on queries loops •Automation of process, Part 11 addressed	•Real time cleaning database •IT solutions are all Part 11 compliant

Knowledge Management: Enablers

	Knowledge Unaware	Knowledge Aware	Localized Sharing	Knowledge Integrated	Knowledge Enabled
Leadership	•Staff do not feel empowered to develop the corporate knowledge base	•Articulated need to improve knowledge management from some senior managers	•Different visions exist for knowledge management • Staff feel empowered to develop & share knowledge at a local level	•Clear enterprise-wide vision for knowledge management • Leaders perform a coaching & mentoring role	•Leaders actively involved in knowledge mgmt. •Leaders are role models for knowledge sharing
Culture & Climate	•No real commitment to knowledge sharing knowledge is power • Little trust within teams	•Pockets of staff share same values/attitudes regarding importance of knowledge	•Behaviors supporting knowledge sharing, re-use and growth within teams • Trust within teams	•Common attitudes towards improving corp. knowledge • Knowledge sharing= power • Physical space supports knowledge sharing	•High levels of trust across the organization • Rewards processes support knowledge sharing behavior
Measures	•No measures for the contribution of intellectual assets	•Some awareness importance intellectual assets • Informal measures to value intellectual assets	•Local measure for the value, contribution and re-use of intellectual assets	•Enterprise-wide intellectual asset measures aligned with business performance measures	•Link between knowledge management & business success clearly articulated •Measures are periodically reviewed
Technology	•Basic communication facilities (*e.g.,* e-mail) • No desktop tools to support knowledge management	•Basic electronic directory of some intellectual assets • IT solutions in isolation	•Desktop tools support knowledge management (*e.g.,* groupware) • Technologies are chosen to meet the needs of small groups	•Consistent standardized database architectures • Advanced desktop tools • Organization-wide e-directory of intel. assets	• Active data mining • Technology chosen on overall need of the business • Sophisticated tools (*e.g.* CBR)
Practices	•No linkage strategy - knowledge • No stds., guidelines, roles or responsibilities for knowledge mgmt.	•Awareness of the need to adopt common practices • Some basic guidelines for knowledge mgmt.	•Local projects initiated to support knowledge management • Local QA activities • Local roles & responsibilities	•Knowledge management program office • Enterprise-wide standards, guidelines, roles & responsibilities	•Knowledge management initiatives tightly linked to business strategy • Active mgmt. of support functions (*e.g.* HR)
Intellectual Assets & Learning	•Intellectual assets viewed as explicit business transaction information •Learning is classroom	•Recognition of the value of tacit & explicit knowledge •Learning is focused on action without reflection	•Many employees share knowledge & desire to make others sensitive about the importance of a global firm knowledge	•Creation of an interactive knowledge database on the intranet	•Active management of the knowledge database •Possibility to follow course concerning the database

Knowledge Management: Processes

	Knowledge Unaware	Knowledge Aware	Localized Sharing	Knowledge Integrated	Knowledge Enabled
Capture	•No mechanism for knowledge capture • Knowledge capture costs seen as an expense	•Non-integrated, *ad-hoc* informal approaches to knowledge capture	•Local processes for capturing tacit and explicit knowledge within a group or department	•Organization-wide knowledge capture processes integrated into core business processes	•Dedicated resources support knowledge capture • Knowledge capture costs seen as an investment
Organize	• No forma mechanisms for •storing, organizing and categorizing knowledge	• Knowledge is loosely organized by subject • No link between knowledge stored & business processes	• Common terms used to organize knowledge at a local level • Local "knowledge maps"	• Standard enterprise-wide taxonomy • Organization "knowledge maps"	•Recognition that the knowledge organization is an important tool for the next processes and studies
Share	• Limited interaction between staff • Knowledge transfer is *ad-hoc* mainly through chance meetings	•Informal mechanisms for sharing knowledge (*e.g.*, communities of interest)	•Local knowledge sharing within teams or to support specific functions	• Cross-functional knowledge sharing	•Best practices and regularly used knowledge identified and shared
Innovate	• *Ad-hoc* innovation • Low levels of connection to customers and the marketplace	• Most big new ideas come from the board • Innovation is the domain of functional & technical specialists	• Portfolio management approach to innovation emerging • Staff encouraged to submit ideas at a local level	• Explicit idea management processes exist and are adhered to • Open style for managing •innovation	•Innovation is embedded as a core value & competency • Diversity of viewpoint is celebrated
Exploit	• No mechanisms exist to support the achievement of business gain from intellectual assets	• Informal *ad-hoc* use and re-use of knowledge assets	•Creation of a knowledge staff	•Knowledge staff transform ideas into new revenue • Productivity gains monitored at the enterprise level	•Regular up dating of the knowledge staff (introduction of new ideas)